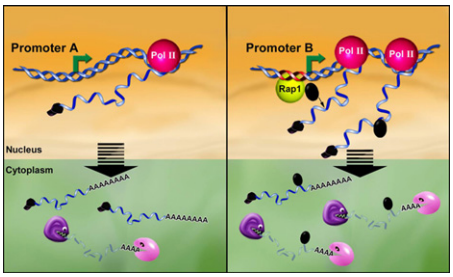
In This Issue

Cell



Promoter DNA Sets mRNA Lifetime

PAGE 1473 and PAGE 1484

mRNA lifetimes are balanced by the rates of pre-mRNA biogenesis in the nucleus and decay in the cytoplasm. Two papers now show that promoter DNA reaches beyond the nucleus to dictate the rate of cytoplasmic mRNA decay. Bregman et al. find that Rap1p binding to promoter sequences stimulates both transcription and decay, and Trcek et al. show that cell-cycle kinases play key roles in bridging promoters and the decay process. This unanticipated link has exciting implications for how cells coordinate and maintain the duration and timing of mRNA expression.

Feeling DisconSIRTed

PAGE 1459

Anxiety behavior in mice is shown by Libert et al. to be increased through the deacetylation of the transcription factor NHLH2 by SIRT1, which elevates the expression of an enzyme involved in the breakdown of serotonin. Extending these results to humans, population studies reveal that single-nucleotide polymorphisms in the *SIRT1* gene are associated with anxiety and psychiatric disorders.

Function for 5hmC

PAGE 1498

5-hydroxymethylcytosine (5hmC), an abundant DNA modification in embryonic stem cells, is thought to represent an intermediate stage in cytosine demethylation, although the functional significance of this modification is still unclear. Yildirim et al. now show that the Mbd3/NURD chromatin regulatory complex preferentially binds to hydroxymethylated DNA and regulates expression of 5hmC-marked genes, suggesting that hydroxymethylation may also serve a specific regulatory function.

Reading Chromatin with Poise

PAGE 1511

Xi et al. show that an H3K9me3-H3K18ac chromatin reader cooperates with Smad proteins to switch chromatin from a poised to an activated state and drive mesendoderm differentiation. They provide structural and biochemical evidence that the chromatin reader, TRIM33, in complex with Smad2/3, binds to poised chromatin, clearing the path for the Smad4-Smad2/3 complex to initiate transcription.

The Right Histones for a Left Brain

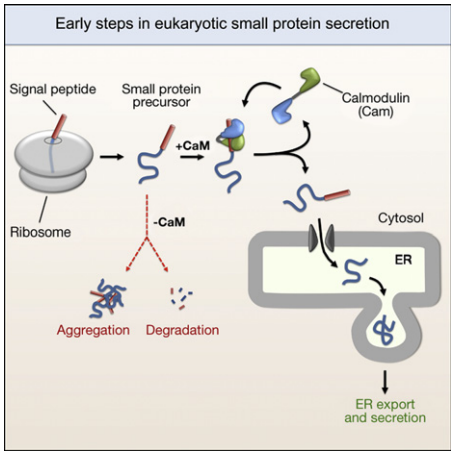
PAGE 1525

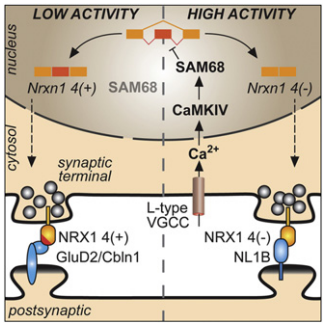
Replication-coupled chromatin assembly maintains stable patterns of gene expression as cells proliferate. Nakano et al. now show that this system can also assign asymmetric identities to daughter cells during *C. elegans* development. Mutations that inhibit nucleosome formation disrupt the bilateral asymmetry of a single pair of neurons, implicating chromatin assembly during replication as a regulator of differentiation.

Calmodulin Looks Out for the Little Guys

PAGE 1576

Secretion of eukaryotic proteins begins with their translocation into the ER in a process involving the signal recognition particle (SRP). The fast translation of very small proteins, however, may not leave enough time for SRP-dependent targeting. Shao and Hegde make the surprising discovery that calmodulin lends a hand to small proteins en route to the ER. The proteins are first released into the cytosol, where transient binding to calmodulin protects them from aggregation and degradation, ensuring translocation into the ER.





Stimulating Synapses Sets Selective Splicing

PAGE 1601

Alternative splicing of synaptic adhesion complexes can generate a cell type-specific code that mediates distinct synaptic connections between neurons. Iijima et al. now show that neuronal activity dynamically regulates alternative splicing of the key *trans*-synaptic adhesion protein neurexin. Calcium-dependent signaling activates the RNA-binding protein SAM68, shifting the alternative splicing pattern of neurexin in the mouse brain and resulting in selective *trans*-synaptic adhesion complexes with postsynaptic receptors.

Fishing out lincRNAs

PAGE 1537

Ulitsky et al. use chromatin marks, poly(A)-site mapping, and RNA-Seq data to identify hundreds of large intervening noncoding RNAs (lincRNAs) in the zebrafish genome and find that only 29 of these have detectable sequence homology with mammalian lincRNAs. The authors show that, despite limited sequence conservation, the functionality of two lincRNAs is retained in their human and mouse orthologs. This study sets up zebrafish as a model for the study of lincRNAs in development and presents a roadmap for identification and analysis of lincRNAs in other model organisms.

piRNAs Prepare for Invasion

PAGE 1551

Piwi-interacting RNAs (piRNAs) play essential roles in genome stability by silencing transposons. Khurana et al. provide insight into how the piRNA pathway adapts to invasion by new transposable elements. They show that, in flies, P element invasion triggers the reactivation of resident transposons. Recovery from the ensuing genome crisis involves the insertion of sequences from the reactivated transposons into piRNA clusters and the production of piRNAs that can silence both the invading elements and the activated resident transposons.

Sectors Wired Up for Allostery

PAGE 1564

Sparse, physically contiguous networks of amino acids, termed sectors, are often organized as three-dimensional "wires" that connect multiple surface sites to the protein active site. Reynolds et al. show that sector-connected surface sites are hot spots that enable allosteric regulation of a protein by a synthetically added regulatory domain. The findings suggest that, by providing a preorganized path for coupling, sectors can facilitate the evolution of intermolecular communication and regulation.

A Goldilocks Approach to Stem Cell Maintenance

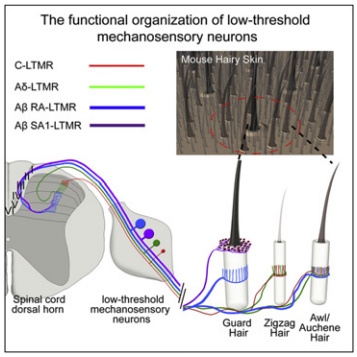
PAGE 1589

Drosophila hemocytes develop in the lymph gland, which contains niche cells, progenitors, and differentiating hemocytes. Mondal et al. find that adenosine deaminase, secreted by differentiating hematocytes as they exit the hematopoietic niche, limits extracellular adenosine levels and reduces adenosine-driven mitogenic signals. The results highlight the complex interactions that are required to maintain the right balance of progenitor and differentiating cells in the hematopoietic niche.

Predicting Combinatorial Control of Chromatin

PAGE 1628

How chromatin regulators (CRs) interact with and remodel chromatin is often studied with chromatin immunoprecipitation followed by sequencing (ChIP-Seq). Ram et al. now report a scalable, multiplex method that identifies antibodies effective for ChIP of chromatin regulators. Using this method, they collect nearly 50 ChIP-Seq data sets and analyze them, uncovering the genome-wide distribution of multiple classes of CRs in human leukemia and ES cells and providing evidence that CRs often assemble in predictable combinations.



Wiring Hair for Touch

PAGE 1615

Different types of mechanosensory neurons mediate touch perception at hair follicles in the skin. Li et al. label individual neurons and study their circuitry in the mouse. They find that different types of hair follicles are innervated by a unique combination of mechanosensory neurons, suggesting that each type of follicle is a functionally distinct mechanosensor. This combinatorial arrangement of neurons may enable the somatosensory system to differentiate among a large variety of tactile stimuli.